COVID-19
ONLINE EDUCATIONAL PROGRAM

Update on COVID-19 Therapeutics

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academic medical education

Disclosures

- **The speaker is a consultant to and has received honoraria and/or research support from the following companies:**
  - Atea
  - Gilead
  - GlaxoSmithKline
  - Merck
  - Novartis
  - ViiV

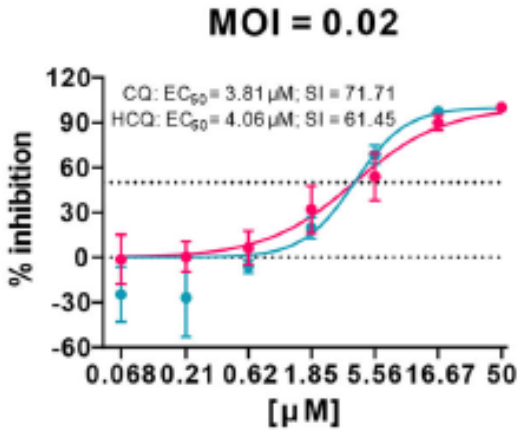
Treatment options for COVID-19

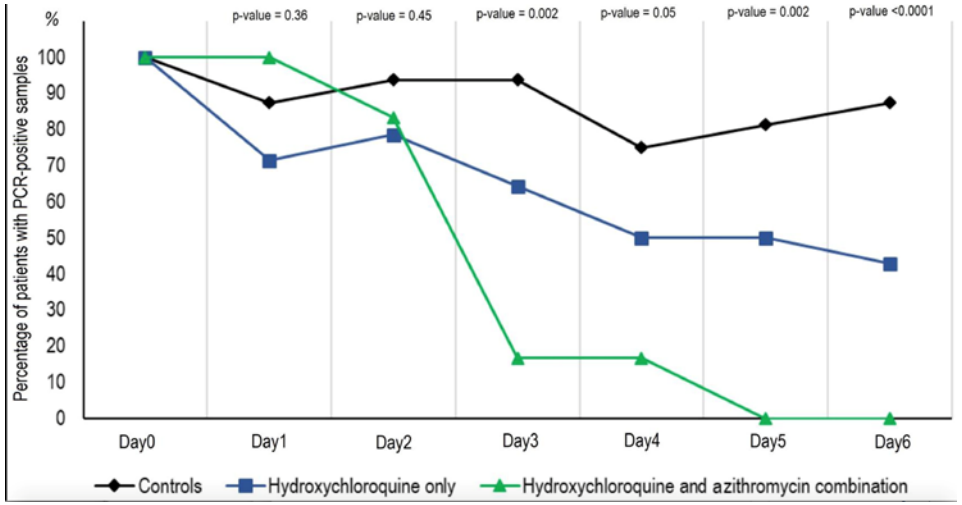
- Antiviral drugs
- Anti-inflammatory drugs
- SARS-CoV-2 antibodies (including convalescent serum)

Hydroxychloroquine

Hydroxychloroquine

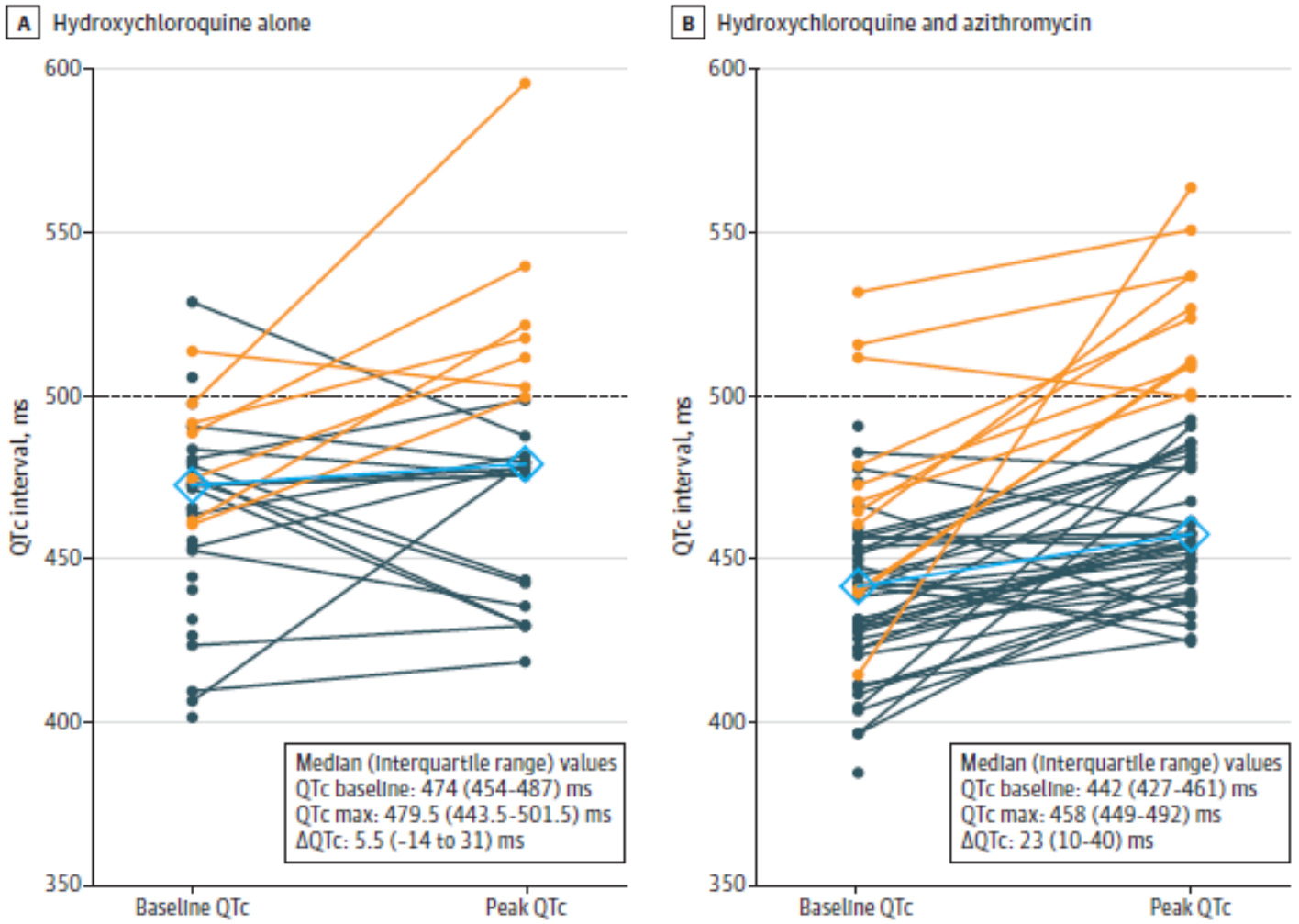
- **Two potential modes of action**
  - Antiviral (inhibits acidification of endosomal vesicles)
  - Anti-inflammatory
- **In vitro evidence for antiviral activity[1]**
- **Mixed results from small clinical trials[2,3,4]**
- **One trial suggests faster reduction of SARS-CoV-2 shedding from oropharynx[4]**





1. Liu J et al Cell Discovery 2020
2. Cortegiani A et al J Crit Care 2020
3. Chen Z et al medRxiv 2020
4. Gautret P et al Int J Antimicrob Agents 2020
5. Molina JM et al Med Mal Infect 2020

QTc prolongation with HCQ ± azithromycin



Mercuro NJ et al JAMA Cardiol 2020

Outcomes of open-label HCQ use in VA hospitals

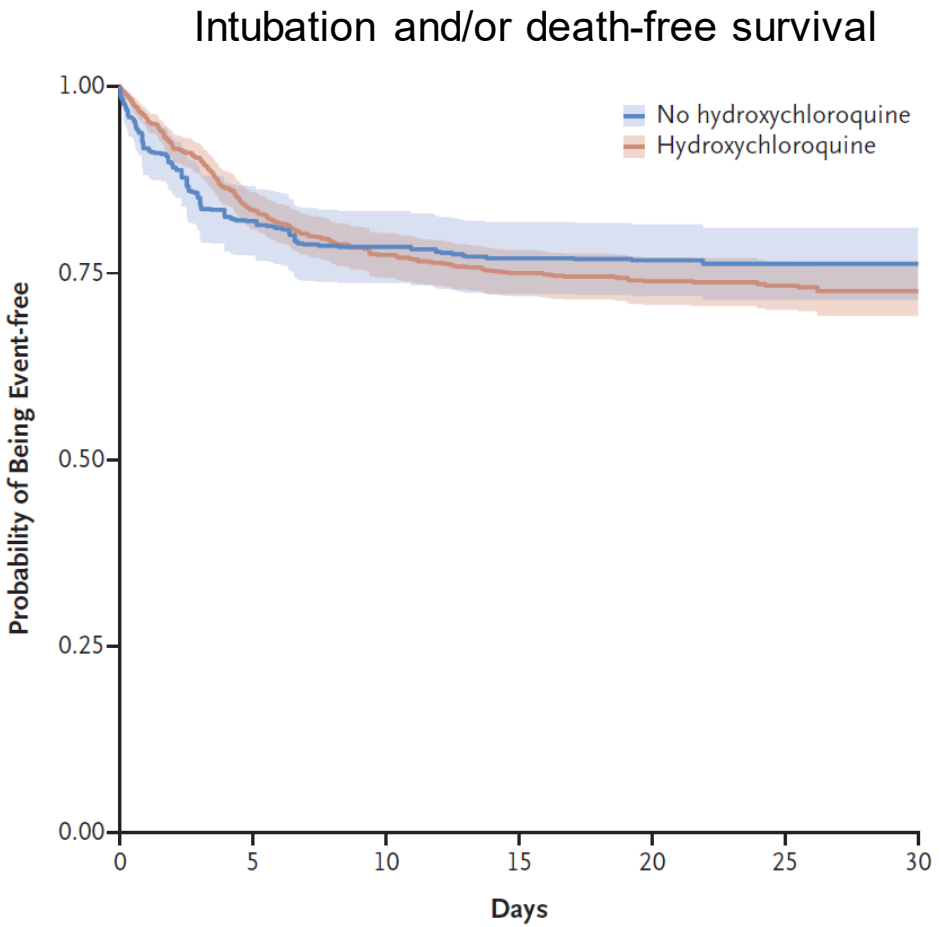
Outcome	HC N=97	HC+AZ N=113	No HC N=158	P value
Death – no. (%)	27 (27.8)	25 (22.1)	18 (11.4)	0.003
Discharge – no. (%)	70 (72.2)	88 (77.9)	140 (88.6)	

HC=hydroxychloroquine; AZ=azithromycin

Magagnoli J et al medRxiv preprint doi: https://doi.org/10.1101/2020.04.16.20065920; posted April 23, 2020.

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

- **Observational study of 1376 consecutive patients in NYC**
  - 811 received HCQ
- **HR for intubation or death = 1.04 (95% CI, 0.82-1.32)**



Geleris J et al N Engl J Med 2020

RECOVERY Trial

- **Large, randomized, placebo-controlled trial of possible treatments for patients admitted to hospital with COVID-19.**
- **More than 11,500 participants have been randomized to the following arms:**
  - Standard of care
  - Hydroxychloroquine
  - Low-dose dexamethasone (6 mg)
  - Lopinavir/ritonavir
  - Azithromycin
  - Tocilizumab
  - Convalescent plasma

RECOVERY hydroxychloroquine trial

- 1542 participants randomized to HCQ versus 3132 to SOC
- No significant difference in primary endpoint of 28-day mortality
- 25.7% for HCQ vs 23.5% for SOC; HR 1.11 (95% CI: 0.98-1.26), p=0.10

RECOVERY Trial HCQ statement 5 June 2020 http://www.recoverytrial.net/

HCQ for post-exposure prophylaxis

- **Randomized, double-blind, placebo-controlled trial**
- **Known exposure to a person with laboratory-confirmed COVID-19**
  - Household contact, HCW, other occupational exposure
  - Enrollment initially within 3 days of exposure, later within 4 days of confirmed SARS-CoV-2 PCR in index case
- **Recruitment in US, Canada via social and traditional media**
- **Remote consent and follow-up**
- **Primary endpoint: symptomatic illness with confirmed molecular test for SARS-CoV-2 or COVID-19-related symptoms**

Boulware DR et al N Engl J Med 2020

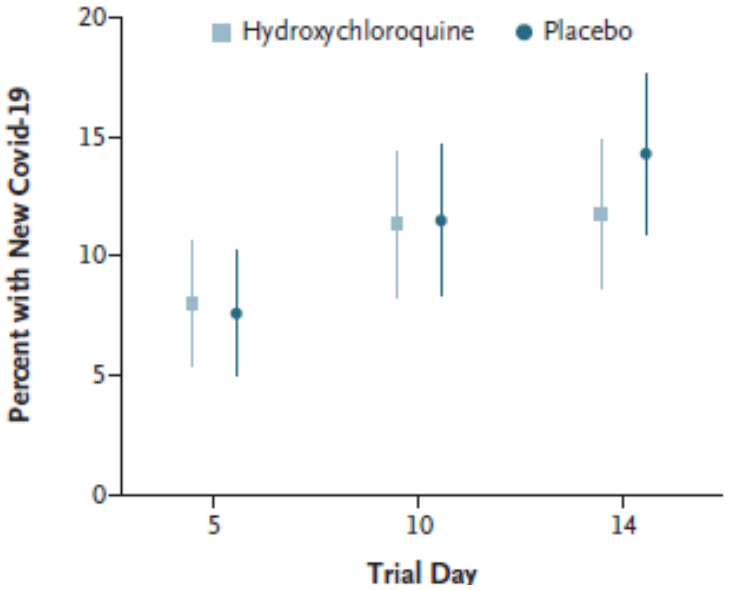
HCQ PEP Study: Results

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Hydroxychloroquine (N=414)	Placebo (N=407)
Median age (IQR) — yr	41 (33–51)	40 (32–50)
Median weight (IQR) — kg	75 (64–86)	76 (64–91)
Female sex — no. (%)†	218 (52.7)	206 (50.6)
Current smoker — no. (%)	15 (3.6)	12 (2.9)
Health care worker — no. (%)	275 (66.4)	270 (66.3)
High-risk exposure — no. (%)‡	365 (88.2)	354 (87.0)
No PPE worn — no. (%)	258 (62.3)	237 (58.2)
Time from exposure to enrollment — no./total no. (%)		
1 day	77/413 (18.6)	63/407 (15.5)
2 days	100/413 (24.2)	106/407 (26.0)
3 days	98/413 (23.7)	117/407 (28.7)
4 days	138/413 (33.4)	121/407 (29.7)
Coexisting conditions — no. (%)		
None	306 (73.9)	290 (71.3)
Hypertension	51 (12.3)	48 (11.8)
Asthma	31 (7.5)	31 (7.6)
Diabetes	12 (2.9)	16 (3.9)

Table 2. Outcomes of Hydroxychloroquine Therapy for Postexposure Prophylaxis against Covid-19.*

Outcome	Hydroxychloroquine (N=414)	Placebo (N=407)	P Value
	number (percent)		
Confirmed or probable Covid-19	49 (11.8)	58 (14.3)	0.35
Laboratory-confirmed diagnosis	11 (2.7)	9 (2.2)	0.82
Symptoms compatible with Covid-19	48 (11.6)	55 (13.5)	0.46
All new symptoms	57 (13.8)	59 (14.5)	0.84
Any hospitalization	1 (0.2)	1 (0.2)	0.99
Death	0	0	—

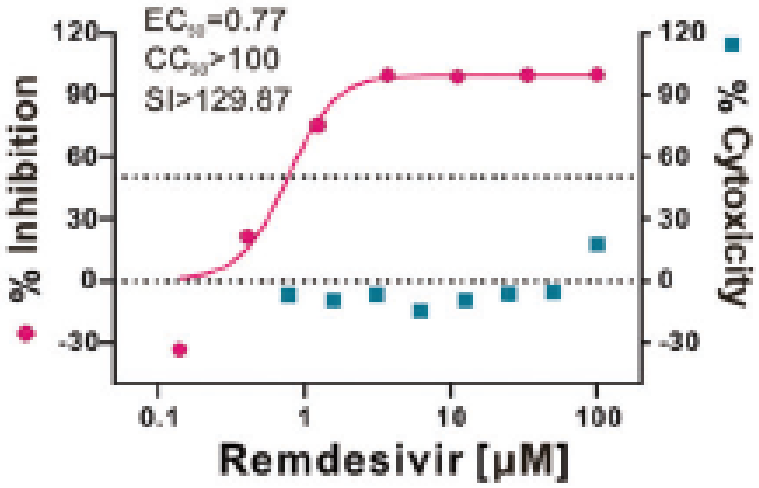


Boulware DR et al N Engl J Med 2020

Remdesivir

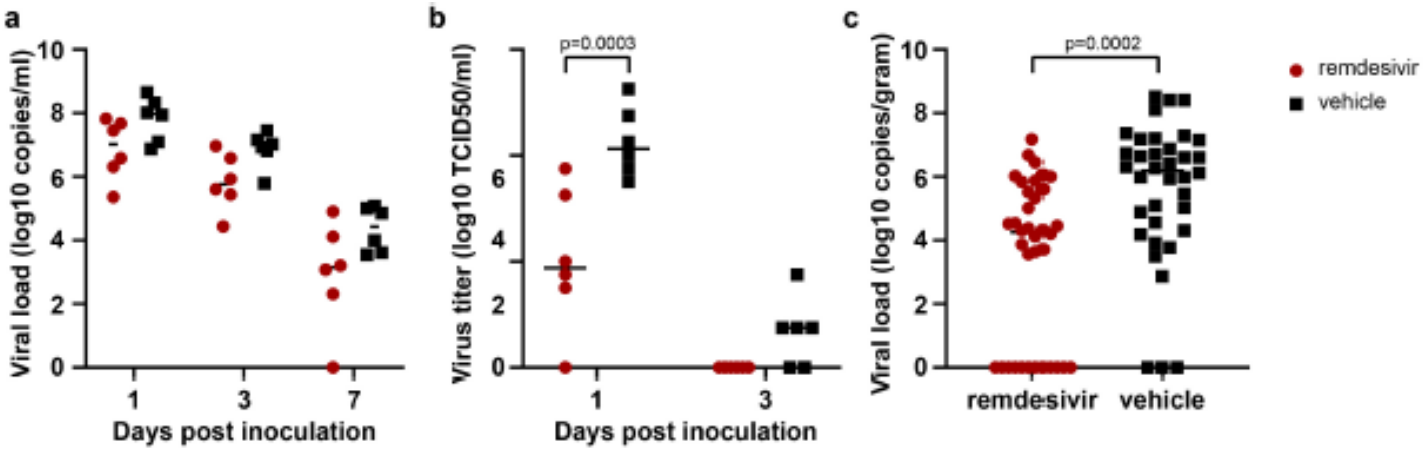
Remdesivir

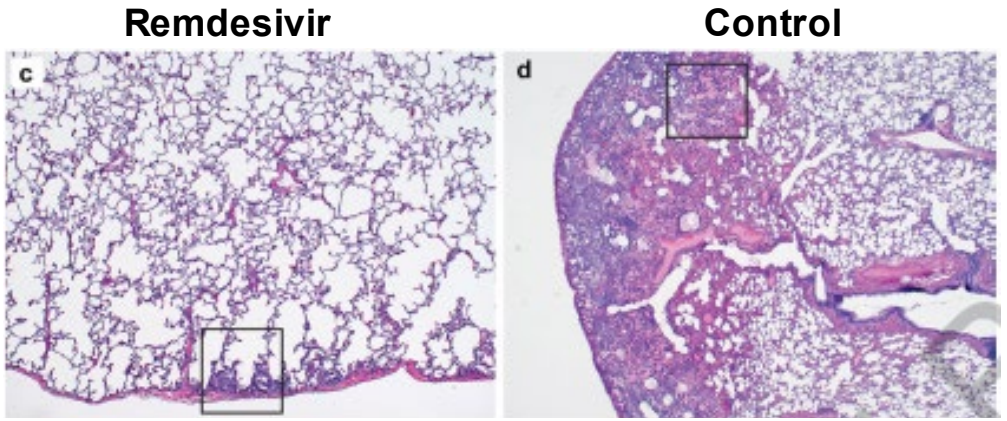
- RNA polymerase inhibitor with in vitro activity against Ebola, SARS, MERS and SARS-CoV-2[1,2]
- Inferior to bNAbs against Ebola[3]
- Effective against MERS in murine and NHP models[1,4]
- Several RCT in moderate and severe COVID-19



1. Sheahan TP et al Nat Commun 2020
2. Wang M et al Cell Res 2020
3. Mulangu S et al N Engl J Med 2019
4. de Witt E et al Proc Nat Acad Sci USA 2020

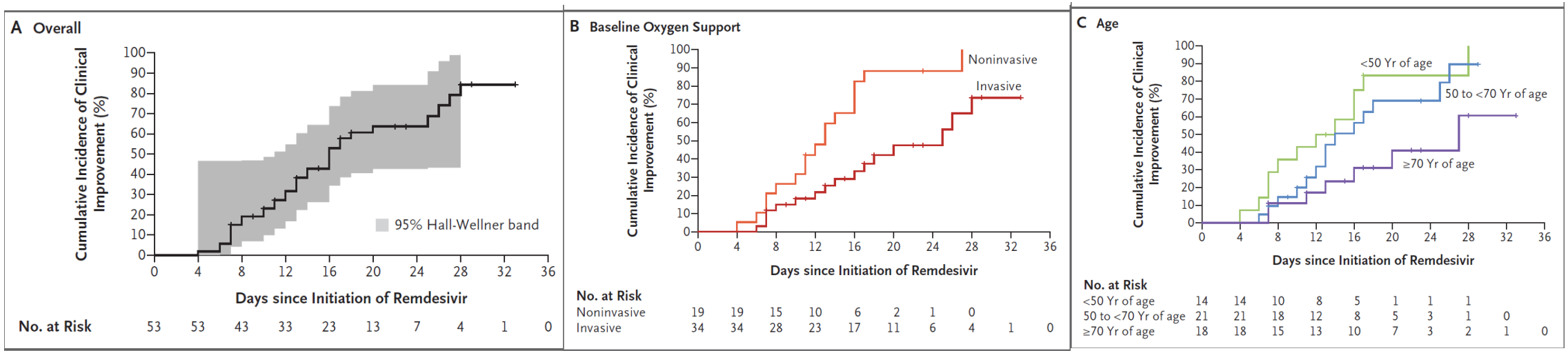
Remdesivir in NHP model of SARS-CoV-2





Williamson BN et al Nature 2020

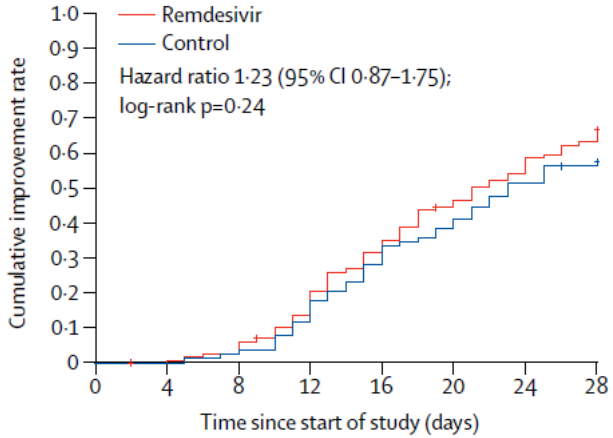
Open-label experience with compassionate-use remdesivir in patients with severe COVID-19

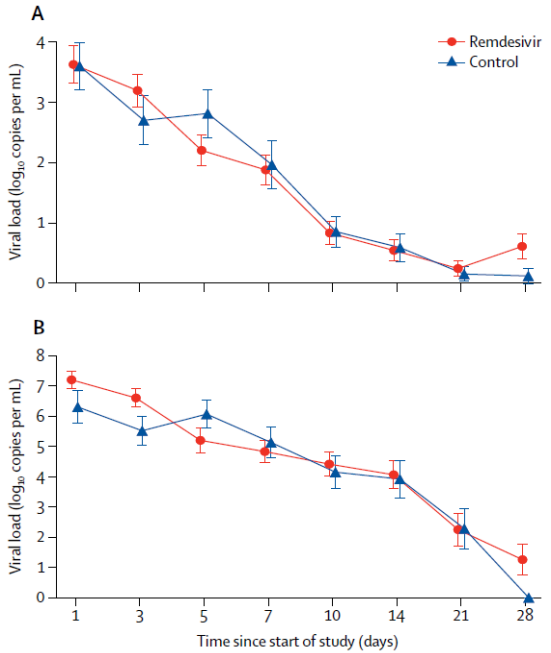


Grein J et al N Engl J Med 2020

Remdesivir in patients with severe COVID-19

- **Double-blind, placebo-controlled RCT**
- **Randomized 2:1 remdesivir vs placebo**
- **Primary outcome: time to clinical improvement by day 28**
- **Enrollment halted due to control of COVID-19 in Wuhan**
  - Only 237 of planned 453 enrolled
  - Power reduced from 80% to 58%

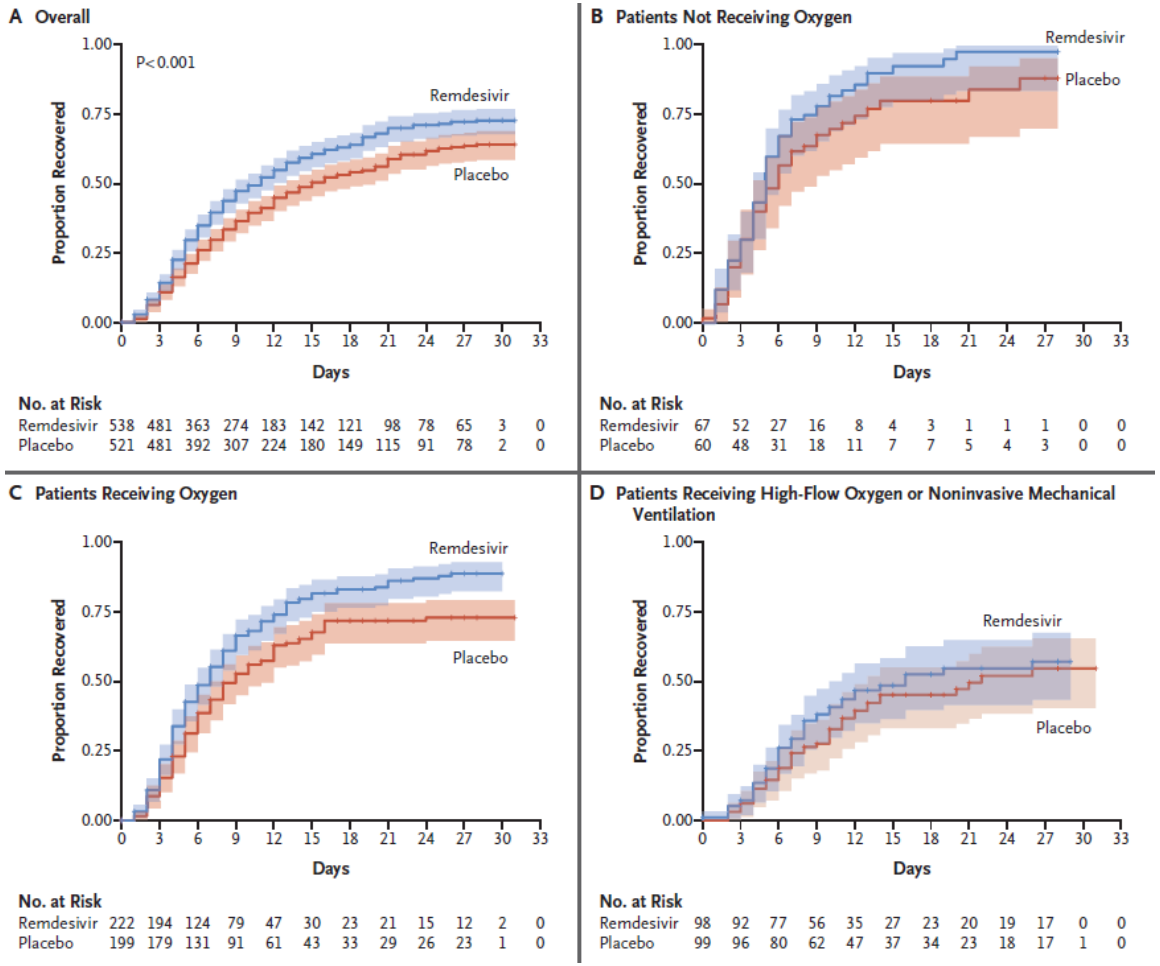




Wang Y et al JAMA 2020

ACTT-1 Study

- **Placebo-controlled, double-blind RCT in hospitalized adults with COVID-19 pneumonia**
- **Participants randomized 1:1 to RDV or placebo**
- **Primary endpoint: time to recovery within 28 days**
  - Preliminary analysis conducted after 606 recoveries were attained

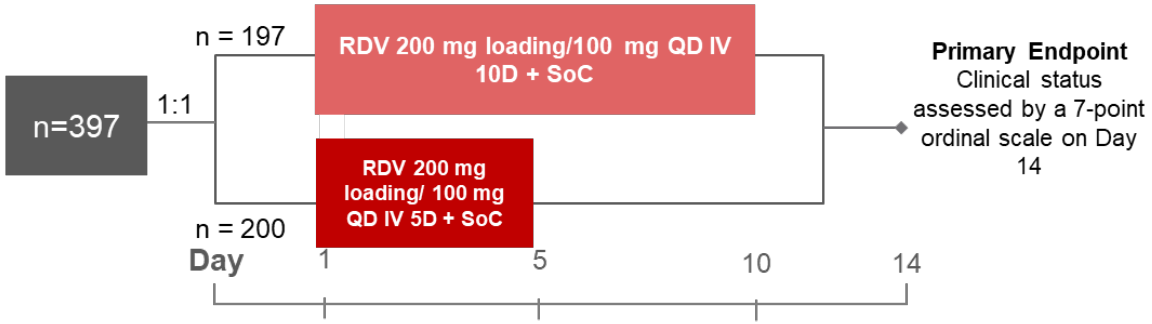


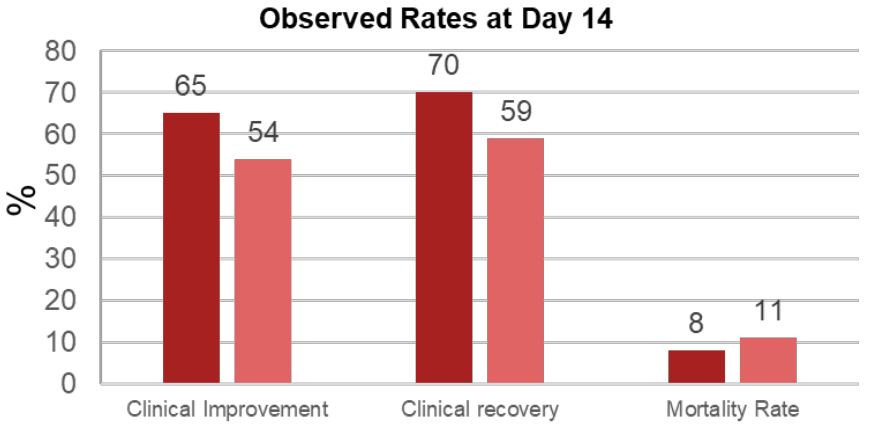
Beigel JH et al N Engl J Med 2020

Remdesevir SIMPLE trial: severe disease

Study GS- US 540-5774

Randomized, open-label, multicenter trial

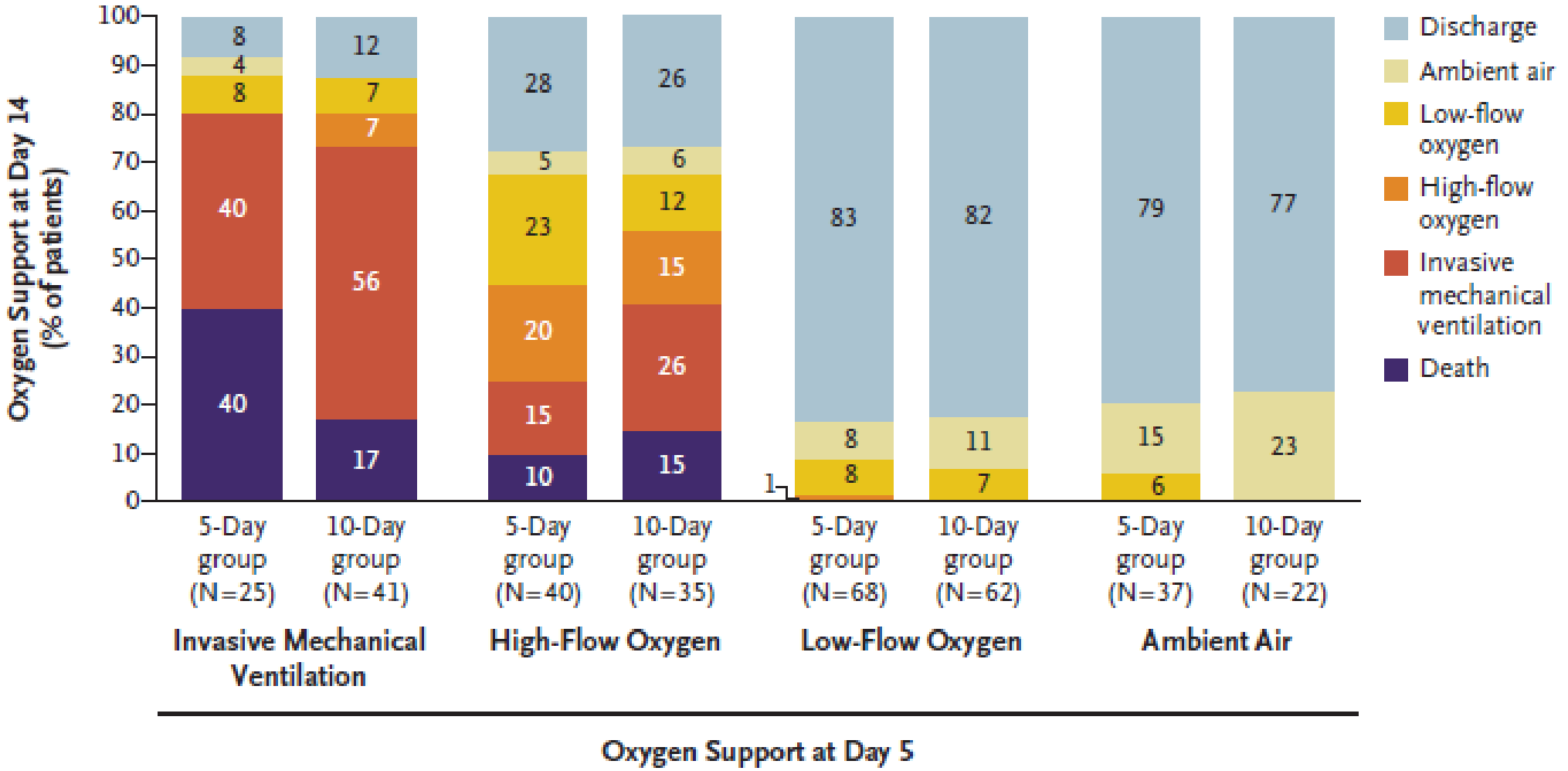




Clinical improvement was defined as an improvement of two or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death. Patients achieved clinical recovery if they no longer required oxygen support or were discharged from the hospital.

Source: Gilead Sciences; Goldman JD et al N Engl J Med 2020.

Remdesevir "severe" trial: change in O_2 support



Goldman JD et al N Engl J Med 2020

Remdesivir SIMPLE trial: moderate disease

- **3-arm, double-blind, placebo-controlled RCT**
  - 5 d vs 10 d vs SOC
- **Entry criteria:**
  - SARS-CoV-2+ PCR
  - SpO2 >94%
- **N=600**
- **Primary endpoint: clinical status at day 11**
- **5-day arm showed greater clinical improvement vs SOC**
  - OR 1.65 [95% CI 1.09-2.48]; p=0.017

	5-Day RDV n=191	10-Day RDV n=193	SOC n=200
Clinical Efficacy Outcomes at Day 11			
≥ 2-point improvement in ordinal scale	134 (70)	126 (65)	121 (61)
≥ 1-point improvement in ordinal scale	146 (76)	135 (70)	132 (66)
Requiring any oxygen support	12 (6)	13 (7)	22 (11)
≥ 1-point worsening in ordinal scale	6 (3)	12 (6)	22 (11)
Death	0	2 (1)	4 (2)
Safety			
Any adverse event (AE)	97 (51)	106 (55)	90 (45)
Grade ≥3 AE	20 (10)	21 (11)	24 (12)
Any serious adverse event (SAE)	8 (4)	7 (4)	18 (9)

Source: Gilead Sciences

Most common Grade 3 or worse AEs in ACTT-1

n (%)	Remdesivir N=538	Placebo N=521
Anemia or decreased hemoglobin	43 (8%)	47 (9%)
Acute kidney injury, decreased eGFR or creatinine renal clearance, or increased blood creatinine	40 (7%)	38 (7%)
Pyrexia	27 (5%)	17 (3%)
Hyperglycemia or increased blood glucose	22 (4%)	17 (3%)
Increased transaminases, including ALT and/or AST	22 (4%)	31 (6%)

Source: Remdesivir EUA fact sheet; Goldman JD et al N Engl J Med 2020

Remdesivir EUA

Remdesivir (GS-5734™) is authorized for use under an EUA only for the treatment of patients with suspected or laboratory-confirmed SARS-CoV-2 infection and severe COVID-19. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen, mechanical ventilation, and/or extracorporeal membrane oxygenation (ECMO). Remdesivir is authorized for adult or pediatric patients who are admitted to a hospital and for whom use of an IV agent is clinically appropriate. Remdesivir must be administered intravenously.

- Must obtain eGFR at baseline
- Should monitor LFTs
- Not recommended for patients with eGFR <30 mL/min
- Must collect and report SAEs and dosing errors

Corticosteroids

RECOVERY dexamethasone trial

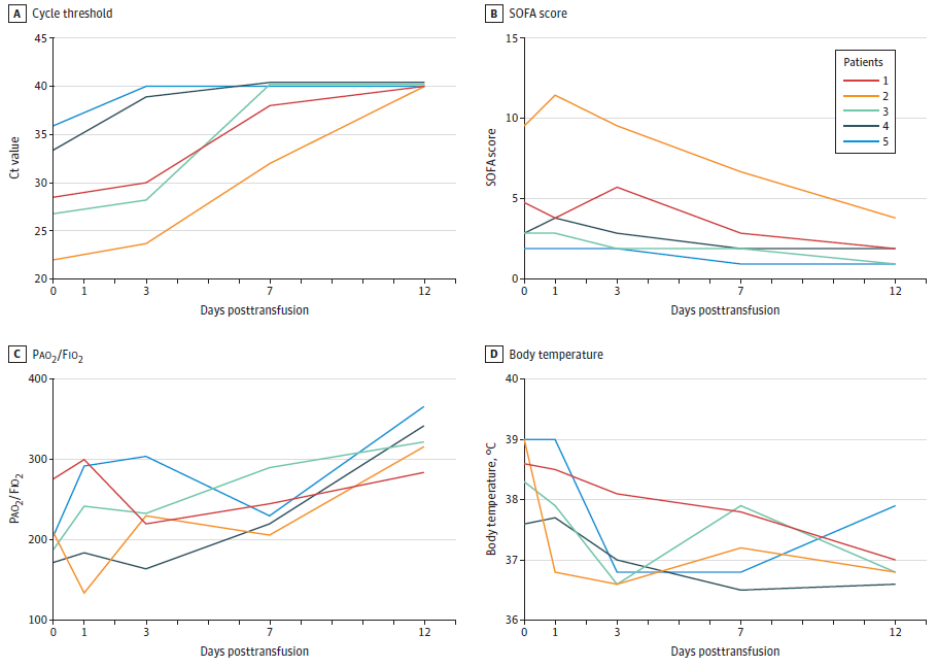
- **2104 participants randomized to dexamethasone 6 mg daily X 10 days versus 4321 randomized to regular care**
- **28-day mortality**
  - Required mechanical ventilation 41%
  - Required supplemental oxygen 25%
  - No respiratory support 13%
- **Reduction in mortality for participants receiving dexamethasone**
  - Mechanical ventilation RR 0.65 [95% CI 0.48 to 0.88]; p=0.0003
  - Supplemental oxygen RR 0.80 [0.67 to 0.96]; p=0.0021
  - No respiratory support RR 1.22 [0.86 to 1.75]; p=0.14

Source: www.recoverytrial.net

Convalscent serum

Convalescent serum

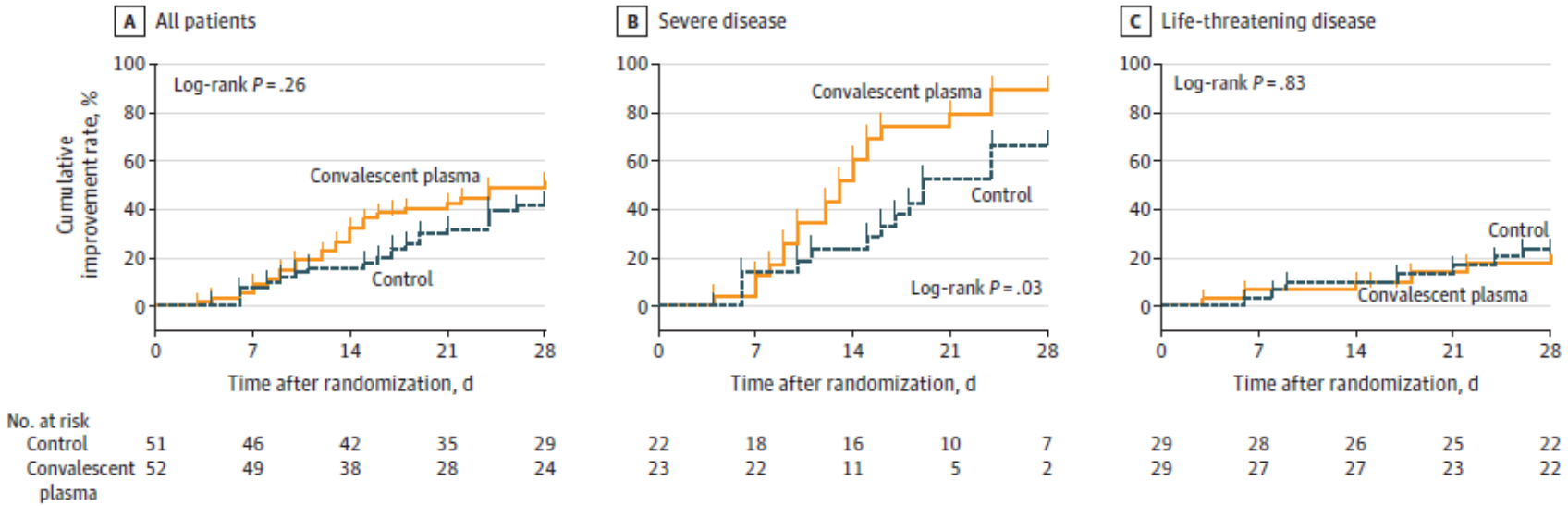
- **Convalescent serum from survivors of COVID-19 infection may contain high titers of neutralizing Ab**
- **Convalescent serum has shown some benefit in treatment of avian (H1N5) and H1N1 influenza and MERS**
- **Uncontrolled pilot study (N=5) suggested possible benefit in patients with COVID-19**
  - 4 of 5 weaned from ventilator
- **Theoretical concerns regarding enhancing antibodies**
- **Clinical trials planned/underway**



Shen C et al JAMA 2020

Phase 2 open-label RCT of convalescent plasma

- 7 medical centers in Wuhan
- 103 participants randomized 1:1 to CP vs SOC
- Plasma units screened for S-RBD-specific IgG titer ≥1:640
- Primary endpoint: time to clinical improvement within 28 days



Li L et al JAMA 2020

Conclusions

- **No compelling evidence for a benefit of hydroxychloroquine in patients hospitalized with COVID-19 or for PEP**
- **Remdesivir reduces time to recovery in patients with moderate and severe disease**
- **Dexamethasone improves survival in patients with COVID-19 who require supplemental oxygen or mechanical ventilation**
- **Convalescent plasma may provide benefit in patients with severe COVID-19**
  - Studies of SARS-CoV-2 mAbs underway